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REVIEW

Natural Compounds: Role in Reversal of Epigenetic Changes

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Abstract—The hallmarks of carcinogenesis are characterized by alterations in the expression of multiple genes that occur via genetic and epigenetic alterations, leading to genome rearrangements and instability. The reversible process of epigenetic regulation, which includes changes in DNA methylation, histone modifications, and alteration in microRNA (miRNA) expression that alter phenotype without any change in the DNA sequence, is recognized as a key mechanism in cancer cell metabolism. Recent advancements in the rapidly evolving field of cancer epigenetics have shown the anticarcinogenic potential of natural compounds targeting epigenetic mechanism as a common molecular approach for cancer treatment. This review summarizes the potential of natural chemopreventive agents to reverse cancer-related epigenetic aberrations by regulating the activity of histone deacetylases, histone acetyltransferases, DNA methyltransferase I, and miRNAs. Furthermore, there is impetus for determining novel and effective chemopreventive strategies, either alone or in combination with other anticancer agents that exhibit similar properties, for improving the therapeutic aspects of cancer.

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Cancer is the second most common disease worldwide. According to Globocan 2012 (http://globocan.iarc.fr), 14.1 million new cancer cases, 8.2 million cancer deaths occurred, and 32.6 million people were living with cancer (within 5 years of diagnosis) worldwide. The majority of the cancer cases occurred in the less developed regions with an estimate of 57% (8 million) new cancer cases and 65% (5.3 million) cancer deaths. Cancer starts and progresses by synchronized genetic and epigenetic alterations, which cause changes in expression of multiple genes or leading to either activation of oncogenes or silencing of tumor suppressor genes [1]. Epigenetics is defined as heritable changes in gene expression caused by chemical modification of genes that do not involve changes in primary DNA sequence. These epigenetic modifications are considered as potential initiating events that occur during early carcinogenesis. Epigenetic mechanisms including chromatin remodeling in an appropriate manner via recruitment of a wide array of chromatin remodeling complex coregulators, effectors, and transcription factors, synthesis of non-coding microRNAs (miRNAs), DNA methylation, as well as covalent modification of histones such as acetylation, deacetylation, phosphorylation, ubiquitination, and sumoylation are considered as important determinants for regulation of gene expression [2].

EPIGENETIC MECHANISMS

DNA Methylation

DNA methylation is the covalent modification of eukaryotic DNA mediated by DNA methyltransferases (DNMT) that transfer methyl groups from S-adenosyl-L-methionine (SAM) to the 5th position of the cytosine pyrimidine ring located predominantly within CpG sequences [3]. The human genome contains CpG-rich regions, known as CpG islands, located in regulatory regions of housekeeping genes, tissue-specific genes, and tumor suppressors, are usually unmethylated in normal cells with the exception of about 6-8% of CGIs methylated in a tissue-specific manner [4].

By contrast, the hypermethylation of repetitive genomic sequences such as ribosomal DNA repeats, satellite repeats, or centromeric repeats prevents chromosomal instability, translocations, and gene disruption by limiting accessibility to the transcription machinery [5].

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These methylation markers are added to DNA by enzymes of the DNMT family. DNMT1, a ubiquitous enzyme, is considered the major methyltransferase that maintains DNA methylation responsible for copying DNA methylation patterns to daughter strands during DNA replication [6]. The other two DNA-methylating enzymes (DNMT3A and DNMT3B) serve as *de novo* methyltransferases that set up DNA methylation patterns early in development [7].

At the same time, the genome of cancer cells undergoes global hypomethylation at repetitive genomic sequences and is associated with genomic instability and chromosomal aberrations [8, 9]. DNA methylation has critical roles in various physiological processes such as X chromosome inactivation, imprinting, and the silencing of germline-specific genes and may affect the transcription of genes by preventing the binding of key transcriptional factors [10]. DNA hypermethylation of promoter CpG islands of tumor suppressor genes leads to transcriptional silencing, which contributes to many of the hallmarks of cancer cells [11].

Histone Modifications

Within the nucleus, DNA is wrapped around a histone octamer formed by four histone partners – an H3-H4 tetramer and two H2A-H2B dimers [12]. Posttranslational modifications at the N-terminal of histones including acetylation, methylation, ubiquitination, phosphorylation, biotinylation, sumoylation, ADP ribosylation, and proline isomerization contribute to genomic stability, DNA damage response, and cell cycle checkpoints integrity affecting gene transcription and DNA repair [13]. These modifications are catalyzed by a variety of histone-modifying enzymes that add or remove specific groups such as histone methyltransferases (HMTs), histone demethylases (HDMs), histone acetyltransferases (HATs), and histone deacetylases (HDACs) [14].

Histone acetylation. Histone acetylation is a highly dynamic process maintained by the interplay of histone acetyltransferases (HATs) and histone deacetylases (HDACs) that acts in opposite manner. HATs use acetyl-CoA as a cofactor and catalyze the transfer of an acetyl group to the ε-amino group of lysine (K) residues in histone tails, neutralizing positive charge on lysine and resulting in a more relaxed chromatin structure, enabling the recruitment of the transcriptional machinery, whereas HDACs reverse the acetylation of lysine residues by catalyzing their transfer to coenzyme A (CoA) to restore their positive charge and stabilize the local chromatin architecture. Hyperacetylation of histone proteins results in activation of normally repressed genes, whereas hypoacetylation leads to silencing of gene transcription [15]. Various regulatory proteins and transcription factors such as p53, E2F, and nuclear factor-κB (NF-κB) involved in stress response, inflammation, and apoptosis are regulated by acetylation [16].

Histone methylation. Histone methylation is a process by which methyl groups are transferred from S-adenosylmethionine (SAM) to lysine and arginine residues of histone proteins of chromosomes, associated with either transcriptional activation, inactivation, or silencing of genomic regions [17]. Histone methylation is mediated by SAM-dependent histone methyl transferases. The effect of histone methylation on gene function and chromatin state is dependent on the methylated lysine residue (e.g. K4, K9, K27, K36, or K79 in H3), the methylation status (mono-, di-, or tri-methylation), and the location (interaction with promoter vs. gene coding regions) [18].

Histone phosphorylation. The process of histone phosphorylation takes place on serine, threonine, and tyrosine residues and is regulated by protein kinases (PKs) and protein phosphatases (PPs) that add and remove the modification, respectively [19]. The modification by histone kinases adds negative charge of the phosphate group from ATP to the histones, which results in repulsive force between them and is therefore associated with transcriptional activation. Phosphorylation of the core histones has been found to be associated with different cellular responses including transcriptional regulation, mitosis, DNA repair, developmental gene regulation, cell cycle progression, chromosome condensation, and apoptosis [20].

Histone ubiquitination and sumoylation. Histone ubiquitination is an enzymatic, posttranslational modification process in which the 76-amino acid protein ubiquitin is attached to a lysine residue of the histone core proteins H2A and H2B via the sequential action of three enzymes, E1 ubiquitin-activating, E2 ubiquitin-conjugating, and E3 ubiquitin-ligase enzymes. The enzyme complex is specific for a substrate and determines the degree of ubiquitination, i.e. either mono- or poly-ubiquitination. Ubiquitination of histones H2A and H2B is associated with different consequences on gene transcription. H2A mono-ubiquitination is considered as a repressive mark, whereas H2B ubiquitination plays an important role in transcription activation and repression. H2B ubiquitination is considered as prerequisite for H3 methylation, but H2A results in inhibition of this methylation [21, 22]. SUMO is a small ubiquitin-related modifier protein of length ~100 amino acids and is attached to the targeted lysine residues of histone protein through an enzyme cascade similar to ubiquitination. Sumoylation of proteins results in a variety of effects including protein stability or enzymatic activity, altered localization, modulation of protein–protein or protein–DNA interactions, or antagonizing other lysine modifications such as ubiquitination, transcription regulation and included transcription factors, transcription machinery associated proteins, and components that modify chromatin structure [23].

Sumoylation of transcriptional activators has been found to be associated with transcriptional repression because of its interaction with other repressor complexes and due to its prevention of histone acetylation, which can be reversed by the action of desumoylating enzymes [24].

Interplay of DNA Methylation and Histone Modifications

In addition to performing their individual roles, interaction of histone modifications and DNA methylation with each other is medicated by a group of proteins with methyl-DNA-binding activity, including methyl-CpG-binding protein 2 (MeCP2), methyl-CpG-binding domain protein 1 (MBD1), and Kaiso, also known as ZBTB 33 (zinc finger and BTB domain-containing protein 33). Localization of these proteins to the promoter of the methylated DNA leads to the recruitment of a protein complex containing histone deacetylases (HDACs) and histone methyltransferases and thus determines gene expression status, chromatin organization, and cellular identity [25]. It has been shown that DNA methylation via several HMTs including G9a, SUV39H1, and PRMT5 to their specific genomic targets led to gene silencing by directly recruiting DNMTs [26-28]. In addition, HMTs and demethylases have also been associated with the regulation of the stability of DNMT proteins, which in turn recruit HDACs and methyl-binding proteins to result in gene silencing and chromatin condensation [29].

miRNA

MicroRNAs (miRNAs) are small non-coding RNAs of 20-22 nucleotides that function in RNA silencing and post transcriptional regulation of gene expression. MicroRNAs are involved in the regulation of biological processes such as cell cycle control, apoptosis, and several developmental and physiological processes including differentiation and development and are altered in cancer development [30]. The involvement of miRNA in suppressing gene expression can arise through numerous mechanisms, including genomic abnormalities, transcriptional regulation, and processing of miRNAs [31]. In addition, controlling the expression of DNMTs and other enzymes associated with epigenetic modifications as well as binding imperfectly to the 3′-untranslated region of the target mRNA leads to aberrant expression, which can affect mRNA translation and stability [32, 33].

Epigenetic Regulation of Gene Expression

Transcriptional deregulation can result in activation of transcription factors associated with oncogenes or silencing of genes responsible for tumor suppression leading to inappropriate gene expression [34]. The characteristic epigenetic markers associated with cancer cells include global hypomethylation, promoter-specific hypermethylation, posttranslational histone modifications, nucleosome remodeling with associated core proteins, global downregulation of miRNA, and upregulation of epigenetic machinery that regulates gene expression [35].

DNA methylation-mediated transcriptional silencing is thought to occur by interfering with the DNA binding of transcriptional factors such as CREB (cAMP response element binding protein), E2F (elongation 2 factor), NF-κB, and AP-2 (activator protein-2) that are unable to recognize specific sequences when they are methylated and by recruitment of methyl-CpG-binding transcriptional repressors, which in turn results in a condensed chromatin state [36]. In addition, methylated DNA can be bound by methyl-CpG-binding domain (MBD) proteins, which are essential for binding to 5-methylcytosine and hinders the binding of transcriptional factors to regulatory elements within promoters and enhancers [37]. These proteins thus help in the recruitment of other proteins such as histone deacetylases that are able to modify the methylation status of histones binding to some specific genetic locus, thereby causing transcriptional silencing of gene expressions.

Histone methylation is associated with different effects of gene activity. Methylation of lysine residue results in either activation or repression of gene activity, whereas arginine methylation leads to silencing of gene transcription. Enrichment of histone methylation at H3K4, H3K36, or H3K79 is generally associated with transcriptional activation. On the other hand, transcriptionally inactive regions are enriched with histone methylation at H3K9, H3K20, or H4K27me [38].

DNA methylation can also direct H3K9 methylation through effector proteins such as MeCP2, thereby establishing a repressive chromatin state [39]. The interactions between DNA methylation machinery and histone modifying enzymes further enhance the complexity of epigenetic regulation of gene expression, which determines and maintains cellular identity and function.

Aberrant miRNA regulation associated with cancer can be influenced by DNA methylation and histone covalent modifications [40]. On the other hand, miRNA targets enzymes of the epigenetic machinery. DNMT1 and DNMT3B are targets of miR-148a in cholangiocarcinoma and cervical cancer, respectively. HDAC1 is targeted by miR-449a and -b in prostate cancer, and HDAC4 by miR-1 in hepatocellular carcinoma [41]. In fact, DNA methylation and miRNA signal transcriptional silencing of associated genes, whereas specific histone modifications and their associated proteins can be characteristic of either gene silencing or gene expression. This review encompasses the various epigenetic changes and the role of natural compounds in their reversal.

ROLE OF NATURAL COMPOUNDS IN EPIGENETIC REVERSAL

The multistage nature of cancer development could potentially be modulated by chemicals that effect cellular enzyme systems, gene expression, signal transduction pathways, differentiation, or interactions with surrounding cells and extracellular matrices. Hence, rationally designed drugs that target a single gene product are unlikely to be of help in preventing or treating cancer. Moreover, theses targeted drugs can cause life-threatening side effects or therapy resistance [42]. When a complex system starts to dysfunction, it is generally best to fix it early, as prevention is better than cure. Often, cancers have a long latency period – 20 years or more. By the time they are clinically detectable, the system has degenerated into a disorganized, chaotic state at which point it may be beyond repair [43]. This has created an urgent need for safe and effective chemopreventive multifunctional drugs that act on entire networks in the body rather than single targets [44].

The basic idea of cancer chemoprevention is to arrest or reverse the progression of premalignant cells towards full malignancy using physiological mechanisms that do not kill healthy cells, but attenuate cancer inflammation [45]. The global demand for more affordable therapeutics and concerns about side effects of commonly used drugs has focused recent research in phytochemicals and traditional medicines that allow chronic use [46]. Natural compounds have been presumed to be safer than synthetic compounds due to their presence in the diet, wide availability, and tolerability. Natural dietary agents including fruits, vegetables, and spices can regulate gene expression via epigenetic mechanisms [47]; they have gained considerable importance owing to their demonstrated ability to suppress cancers. Epidemiological studies have shown that consumption of food rich in fruits, vegetables, and spices can effectively lower the incidence of cancers, indicating correlation between increased intake of dietary antioxidants and associated lower incidence of cancer mortality and morbidity [48, 49]. The reversible nature of epigenetic markers has led to great demand for the identification and development of natural compounds as epigenetic modulators for the prevention of cancer to restore "normal epigenome" [50, 51].

Natural Compounds Affecting the Epigenome

Accumulated evidence shows that natural compounds are associated with numerous health benefits along with their high potential for application in oncology owing to their anticarcinogenic properties [52]. Studies on natural bioactive compounds include plant secondary metabolites such as phytochemicals extracted as natural products from fruits, vegetables, spices and traditional medicinal herbs are associated with the regulation of multiple cancer-inflammation pathways, and epigenetic cofactors can be used in anticancer therapy because of its wide availability, low toxicity, and cost effective measures [53].

A variety of botanical species and plant parts are known for their chemopreventive potential, as they possess antiinflammatory, antioxidant, antiallergic, antiviral, and anticancer activities [54]. It has been shown that dietary agents and non-nutritional components of fruits and vegetables can regulate epigenetic-related mechanisms via initiation of apoptosis, repression of cancer-related genes, reactivation of tumor suppressor genes, cell cycle regulation, and the activation of cell survival protein in different cancers [55, 56].

The interference of multistage carcinogenesis by natural compounds may include their effects on detoxifying and antioxidant enzyme system, induction of antimetastasis response by targeting specific key transcription factors such as activation protein (AP-1), nuclear factor erythroid 2-related factor (NRF2), hypoxia inducible factor-1 (HIF-1) and NF-κB, inhibition of the mitogen-activated proteins (MAPKs)-, protein kinases and growth-factor receptor-mediated pathways, cell cycle arrest, induction of apoptosis, epigenetic cofactors, and microRNAs associated with tumor development and progression [57, 58]. Several natural compounds have been found to play an important role in the reversal of epigenetic changes.

Quercetin. Quercetin is strong natural antioxidant flavonol ubiquitously present in dietary plant sources such as fruits and vegetables, particularly citrus fruits, apples, onions, parsley, sage, tea, red wine, leaves, and grains. The properties underlying the antioxidant activity of quercetin may include oxygen radical scavenging, xanthine oxidase inhibition, protection against lipid peroxidation *in vitro*, and formation of inert complexes by chelating metal ions that cannot take part in the conversion of superoxide radicals and hydrogen peroxide into hydroxyl radicals [59]. The anticancer efficacy of quercetin has been linked to the modulation of mitogenic signaling, cell-cycle regulation, survival/apoptotic signaling, angiogenic, and metastatic events in cancer cells, with limited or no toxicity against normal cells.

Quercetin has been shown to have effect on histone acetylation. Quercetin decreases the level of COX-2 (cyclooxygenase-2) protein by blocking the binding of different transcription activators such as CREB2, NF-κB, p300, and c-Jun to the promoter of proinflammatory gene *COX2*, which accounts for its anticancer activity [60].

It has been reported that quercetin increases deacetylase activity of recombinant SIRT1, but on the other hand, it inhibits SIRT1 activity at the cellular level [61]. This biphasic effect on the activity of class III histone deacetylase SIRTs can be explained by metabolic transformation of quercetin. Ingestion of quercetin-3-O-

glucuronide, a quercetin metabolite, leads to inhibitory function on recombinant SIRT-1. SIRT1-induced apoptosis in response to TNF-α (tumor necrosis factor alpha) suppresses transcription of NF-κB-regulated genes by deacetylating RelA/p65 at lysine 310 [62].

Quercetin induces FasL-dependent apoptosis through promotion of acetylation of histone H3 in leukemia HL60 cells by activating HAT and inhibiting HDAC, which results in activation of ERK (extracellular signal-regulated kinase) and JNK (jun N-terminus kinase) signaling pathways. Quercetin in human leukemia HL-60 cells induces significant histone hyperacetylation, indicating that its *in vitro* anticancer activity is linked to histone hyperacetylation [63]. Quercetin also activates signaling pathways by induction of the phosphorylation of ATM and H2AX [64].

Quercetin showed a concentration-dependent effect on hypermethylation of $p16^{INK4a}$, a tumor suppressor gene, in human colon cancer cell line RKO. It resulted in the reversal of hypermethylation after 120 h of treatment, expressing the influence of quercetin on DNA as well as protein methylation levels [65].

A study has revealed inhibition activity of quercetin against demethylase LSD1. This may result in controlling the gene transcription associated with cell growth and differentiation and is of potential therapeutic value [66]. Quercetin and other catechol polyphenols can inhibit DNMTs and thus DNA methylation indirectly through changing concentrations of SAM and SAH (S-adenosyl-L-homocysteine) intracellularly in a specific manner [67].

EGCG. Epigallocatechin gallate (EGCG), also known as epigallocatechin-3-gallate, is the ester of epigallocatechin and gallic acid and is the most abundant catechin in green tea, accounting for more than 50% of the active compounds present in green tea. Studies have shown that polyphenolic compounds, green tea catechins, can reduce the risks of diseases associated with cancer. Other major green tea catechins include (–)-epicatechin-3-gallate (ECG), (–)-epigallocatechin (EGC), and (–)-epicatechin (EC) [68]. EGCG is a powerful radical scavengers and acts as a pro- and antioxidant, triggers signal-transduction pathways, and induces the expression of phase II detoxifying and antioxidant enzymes such as glutathione peroxidase (GPx), glutathione, and many other enzymes. It is known to inhibit carcinogenesis by modulating some signal transduction pathways including JAK/STAT, Wnt, and Notch [69].

Studies have shown EGCG to have various properties that could give it anticancer activity that may include several different mechanisms based on modifications of epigenetic processes, particularly in cancer cells, which can be altered by the epigenetic machinery. They include apoptosis induction, regulation of signal transduction pathway, inhibition of oxidative stress and angiogenesis, cell cycle arrest, and reduction of cancer cell proliferation [70, 71].

EGCG showed a direct inhibitory effect on the activity of the DNMT1 molecule through the formation of hydrogen bonds on binding with different residues in the catalytic pocket of DNMT stabilized by Mg^{2+} [72]. An indirect inhibitory effect of EGCG on DNMT1 is due to that compounds with a catechol group are excellent substrates for methylation mediated by catechol-O-methyltransferase (COMT), which results in depletion of the methyl donor SAM and formation of SAH, a potent feedback inhibitor of DNA methylation considered also as a potential demethylating agent.

EGCG effects at physiologically attainable concentrations have been shown to be associated with demethylation of specific promoters of genes including p16, MGMT, hMLH1 (human mutL homolog 1), GSTP1 (glutathione S-transferase Pi), and/or RARβ in various cancer cell lines [73]. Treating LNCaP cells with EGCG decreases transcriptional gene activity coding for HDACs 1-3 and thus decreases protein levels that are associated with increased acetylation level of lysines 9 and 18 on H3 histone and H4 histone related amino acid residues as well [74].

Recent studies involving human epidermoid carcinoma cells A431 revealed that treatment of these cells with EGCG results in re-expression of silenced tumor suppressor gene p16(INK4a) and p21/Cip1 mRNA and proteins through decreasing DNA methylation level of lysine 9 on histone 3 (H3-K9) and also associated with their effect on DNMT activity. On treating cells with EGCG at different concentrations (5-20 μM), decreased levels of 5-methyl-cytosine, DNMT activity, mRNA and protein levels of DNMT1, DNMT3a, and DNMT3b was expected, but treatment with these concentration showed increased acetylation of lysines 9 and 14 on H3 histone (H3-K9 and -K14) and acetylated lysine 5, 12, and 16 on H4 histone [75].

Treating AsPC-1 pancreatic metastatic adenocarcinoma cells with EGCG also inhibits HDAC activity, which in turn induces Raf kinase inhibitor protein (RKIP) via repressing ERK activation and upregulated E-cadherin expression. This leads to increase in histone H3 expression and inhibition of NF-κB nuclear translocation, Snail (zinc finger protein SNAI1) expression, and MMP-2 and-9 activities contributing to decreased metastatic potential of AsPC-1 cells [76].

EGCG treatment on human colon carcinoma HT29 cells showed a significant dose-dependent inhibition of HDAC activity and HDAC1 protein expression. In addition, this treatment also reversed the aberrant hypermethylation status of tumor suppressor gene *RECK* and thus enhanced mRNA expression significantly [77].

Experiments conducted with EGCG on prostate cancer cell lines LNCaP and PC-3 showed dose- and time-dependent inhibition of class I HDACs associated with increased histone H3 and p53 acetylation. Acetylation of p53 at Lys373 and Lys382 resulted in p53

accumulation in the G0/G1 cell cycle phase due to block of its MDM-2-mediated ubiquitination, which then binds with the *p21* and *BAX* gene promoters leading to apoptosis induction, suggesting proteasomal degradation of class I HDACs by EGCG [78].

The inhibitory influences on HATs by EGCG at 50 μM may ultimately suppress agonist-dependent androgen receptor (AR) activation by downregulation of its acetylation, and it is thus considered beneficial to hormone-dependent prostate cancer. AR remains "locked" in the cytoplasm, which provides transcriptional silencing of AR-related genes. Acetylation of AR by p300/CBP and PCAF (HAT KAT2B)/TIP60 (HAT KAT5) supports the understanding that HAT coactivators compete with HDAC corepressors for binding to promoter regions and/or protein substrates and determine the level of transcription [79].

In addition to study the influence of EGCG on HDACs, it has also been identified as a HAT inhibitor with global specificity for the majority of HAT enzymes. Inhibitory effect of 90% on HAT activity was observed on treating HeLa cell nuclear extract with 100 μM EGCG, with no change in HDAC, SIRT1, and histone methyltransferase activities. Hypoacetylation of RelA (p65) on inhibition of NF-κB activation by EGCG resulted in increased level of cytosolic IκBα, which in turn prevents p65 translocation into the nucleus, thus interrupting the TNFα-induced cascade of events [80]. In addition, EGCG has been found to demethylate the promoter of the *Wnt* oncogene in lung cells [81].

EGCG alone or in combination other epigenetic-modifying compounds such as HDAC inhibitors can be considered as effective anticancer agents and have led to great attention to the development of an epigenetic diet for cancer prevention [82].

Curcumin. The phytochemical curcumin (1,7-bis(4-hydroxy-3-methoxy-phenyl)-1,6-heptadiene-3,5-dione) is a biologically active phenolic component of *Curcuma longa* (turmeric). It has long been used in traditional Indian Ayurvedic medicine [83]. Curcumin has many pharmacological effects and possesses antioxidative, anti-inflammatory, antiproliferative, antiangiogenic, and anticancer properties, thus being used as a therapeutic anticancer agent [84].

It is considered as nontoxic and has been shown to suppress tumor growth through multiple signaling pathways by regulation of expression of various proteins including NF-κB, Akt, MAPK, p53, Nrf2, Notch-1, JAK/STAT, β-catenin, and AMPK (5′-AMP-activated protein kinase). The anticancer efficacy of curcumin has been linked to the modulation of mitogenic signaling, cell-cycle regulation, survival/apoptotic signaling, angiogenic, and metastatic events in cancer cells [85]. Pharmacokinetic analyses have shown that human plasma contains a low concentration of curcumin compared with measured concentration in experimental cell culture systems, which might be related to its biological effect through remodeling of the epigenome network. Curcumin is considered a strong epigenome modulator and functions as a histone-modifying compound, thereby acting as an inhibitor of HDAC and HAT [86].

In 2004, curcumin, in its physiological range, was reported to be a specific inhibitor of p300/CREB-binding protein (CBP) HAT activity in HeLa cervical cancer cell line, while there is no change in p300/CBP-associated factors, histone deacetylase HDAC1, and histone methyltransferases. As a consequence, acetylation of histones H3 and H4 is inhibited with the most potent inhibitory IC_{50} concentration of 25 μM, which in turn inhibited p300-mediated acetylation of p53 [87]. It also promotes proteasomal degradation of p300 and CBP with no effects on the HATs PCAF or GCN5 [88].

It has been shown that curcumin induces cell cycle arrest and apoptosis of numerous cancer cell lines, which is mainly attributed to the NF-κB and PI3K/AKT signaling pathway [89]. NF-κB, which is known as a proinflammatory transcription factor, contributed to the activation of different genes involved in various cellular processes as it undergoes acetylation with p300/CBP acetyltransferases at multiple lysine residues on histone. It has been reported that treating cancer cells with curcumin could significantly reduce HAT activity, p300 levels, and acetylated CBP/p300 gene expression, and consequently suppressed NF-κB binding, thus contributing to its potent NF-κB inhibitory activity [90].

The ability of HDAC inhibitors to alter various cellular functions that are deregulated in cancer cells enables them to be used as cancer therapeutic compounds [91]. Various studies have revealed the influence of curcumin on HDAC expression. Curcumin is found to be a more potent HDAC inhibitor than sodium butyrate and valproic acid, which are well-known HDAC inhibitors. It has been reported that curcumin treatment can lead to significant decrease in protein levels of HDAC 1, 3, and 8, thereby increasing acetylation level of histone H4 [92].

The contradicting effect of curcumin on different subtypes of HDAC enzymes requires better understanding of the mechanism involved in HDAC expression on curcumin treatment [93]. Curcumin also showed potent activity as an inhibitor of HDAC in medulloblastoma cells, and it directly inhibited HDAC4 transcription [94].

Numerous animal studies have shown *in vitro* inhibition of HATs and HDACs in different cancer models. Evidences suggesting the inhibition of both HATs and HDACs together might provide a novel strategy to prevent cancer [95]. Curcumin induces epigenetic modifications via modulating DNA methylation and is considered as an effective hypomethylating agent decreasing DNMT activity, thus facilitating inactive prometastatic and proto-oncogene expressions. Curcumin inhibits DNMT activity by interacting directly with *Sss*I methyltransferase, a homolog of DNMT1, and covalently blocks the

catalytic thiolate of C1226 of DNMT1, which inhibits DNMT1 catalytic activity [86, 96].

In a breast cancer cell line at 10 μM concentration, curcumin induced significant decrease in protein levels of DNMT1, HDAC1, and MeCP2 as well as in the transcriptional levels of all three DNMTs, thereby reversing epigenetic modifications through preventing the binding of NF-κB/Sp1 binding to the promoter region of *DNMT1* [97].

Curcumin showed epigenomic effects by inducing global DNA hypomethylation in MV4-11 leukemia cells and decreasing (by 15-20%) DNMT1 expression in an acute myeloid leukemia (AML) cell line MV4-11 model with IC_{50} of 3 μM after 72 h treatment. This effect may be associated with reactivation of tumor suppressor gene p15INK4B (p15) through promoter hypomethylation, G1 cell cycle arrest, and *in vitro* induction of apoptosis [98]. Curcumin has been found to demethylate and reactivate tumor suppressor genes RARβ2 and WIF-1 in human cervical and non-small-cell lung cancer cells, respectively [99, 100]. In addition, it may lead to *NEUROG1* and *NRF1* promoter demethylation and re-expression in human prostate cancer cells [101, 102].

Treating selected colorectal cancer cell lines HCT116, HT29, and RKO with curcumin changed methylation pattern at selected partially methylated loci rather than completely methylated CpG sites [103]. It has been reported to selectively induce *NRF2* and *RARβ2* gene promoter demethylation [104]. In MDA-MB-435 cells, curcumin has been found to downregulate EZH2 expression and thus reduced methylation of H3K27me3 [105]. Studies also showed induction of antiinflammatory effects of curcumin and suggest correlation between inflammation and epigenetic alterations that occurs during tumorigenesis [106].

Curcumin has been found to alter miRNA expression in BxPC-3 pancreatic cancer cell line via upregulation of tumor suppressor miR-22 and downregulation of oncogenic miR-199a, while the upregulation of miR-22 is associated with suppression of the target gene *Sp1* and *Era* expressions. In contrast, curcumin has also been found to suppress miR-21 expression and thus induce tumor suppressor PTEN [107]. Exposure of MCF-7 breast cancer cells to curcumin can lead to increase in the levels of proapoptotic miR-15a and miR-16 accompanied by suppression of the expression of their target gene *Bcl-2* [108].

Low bioavailability of curcumin due to its insolubility and instability in water may lead to an issue of concern of use of curcumin as a bioactive agent in chemotherapy. It can be enhanced by utilizing properties of dietary factors such as rubusoside, found in Chinese blackberry extract, as well as compounds such as phosphatidylcholine, found in soy and egg yolks, thus increasing its therapeutic potential in cancer prevention [109].

Genistein. Genistein (4′,5,7-trihydroxyisoflavone) is a phytoestrogen belonging to a class of polyphenolic flavonoids primarily abundant in soybeans [110]. This polyphenol has been shown to act as chemopreventive agent against several cancer types, particularly hormone-responsive breast and prostate malignancies attributed to the hormonal activity mediated by binding to estrogen receptor, ER-α, and ER-β, as well as androgen receptor downregulation in androgen-dependent prostate cancer cell lines such as LNCaP [111, 112]. Exposure to moderate doses of genistein induced inhibitory effects on cervical, prostate, colon, and esophageal cancers with the associated mechanism contributing to its anticancer properties including carcinogen bioactivation, cell-signaling, cell cycle regulation, angiogenesis, oxidative stress, inflammation, and gene transcription regulation by affecting epigenetic mechanisms that are altered in cancer cells [113, 114].

Genistein is only a moderately strong radical scavenger, thus exerting its antioxidant effects at low concentrations corresponding to the relevant physiological concentrations in plasma genistein shown to have inhibitory effect on cellular growth followed by apoptosis in various hematological cancer cell lines and cell lines of solid tumor origin (e.g. HCT-116 and SW-480) [115]. Its effect on cell cycle is commonly associated with induction of G2/M cell cycle arrest in breast, colon, malignant glioma, and prostate cancer cell lines [116, 117].

Genistein is also a potent modulator of epigenetic markers (including DNA methylation and/or covalent histone modifications), acting either directly or through a steroid receptor-dependent process. Treatment with genistein (10-25 μM) on prostate cell lines LNCaP and DuPro promotes hyperacetylation of histones H3 and H4 associated with increased H3K4 acetylation at tumor suppressor genes p16INK4a and p21WAF1/CIP1 transcription start sites, resulting in increased expression of transcriptional activating HATs and thus subsequent re-expression [118].

In vivo experiments on a murine orthotopic breast cancer model supplemented with genistein-enriched diet showed inhibition of cancer growth with considerable lower net weight of tumor and significantly less proliferating cell nuclear antigen-positive cells compared with tumors developed in animals fed with a genistein-free diet. Genistein effects the epigenome at mRNA level via increasing tumor suppressor genes p16 and p21 expression and downregulating oncogenes BMI1 (polycomb complex protein BMI-1) and c-MYC. It also increased acetylation of histone H3 and H3K4me3. On the other side, formation of suppressive chromatin markers H3K9me3 and H3K27me3 was decreased. The more prominent changes were seen in precancerous breast cell line, whereas breast cancer cells exhibited mild changes [119].

Treatment of ER-α positive, MCF-7 and ER-α negative MDA-MB 231 breast cancer cell line with 18.5 μM concentration of genistein showed decrease in trimethy-

Natural compounds playing important role in reversal of epigenetic changes

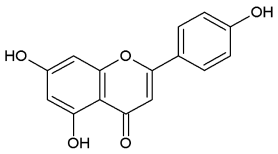
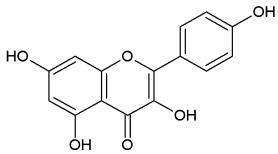
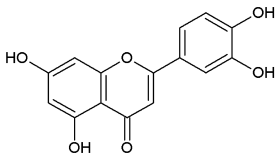
Natural compound	Structure	Natural source	Pharmacological effects	Model	Epigenetic mechanism of action
1	2	3	4	5	6
Polyphenols and other natural compounds					
Apigenin		Chinese cabbage, garlic, barley, olive oil, chamomile, apples, onion	anticancer, antioxidant, antiproliferative, anti-angiogenesis and anti-migration [126]	prostate cancer cells PC-3 and 22Rv1	inhibition of class I HDACs (particularly HDAC1 and HDAC3); global histone H3 and H4 acetylation, as well as localized hyperacetylation of histone H3 on the p21 promoter [127]
Kaempferol		tea, kale, carrot, capers, leek, celery, apples	antioxidant, anti-inflammatory and anticancer [128]	liver and colon cancer cell (HepG2, Hep3B, HCT116)	pan-inhibitor of human HDACs of classes I, II and IV; hyperacetylation of histone H3 complex [129]
				chronic myelogenous K562 and promyelocitic U937 leukemia cell	increased expression of deacetylase SIRT3 and its mitochondrial localization associated with PI3K inhibition; dephosphorylation of Akt at Ser473 and Thr308 [130]
Luteolin		sage, thyme, peppermint, carrot, broccoli, onion, chilli	anti-estrogenic, antioxidant, anticancer, anti-inflammation, anti-metastasis, anti-angiogenesis [131]	LNM35, HT29, HepG2, MCF7/6 and MDA-MB231-1833 cells	regulation of gene expression via inhibition of total HDAC activity associated with increased acetylation of histones H3 and H4 [132]
				PC-3 cells	inhibiting Aurora B kinase activity, thus, reducing histone H3 phosphorylation; down-regulated acetylation status of histone H4 at pro-proliferative kinase PLK-1 promoter [133]

Table (Contd.)

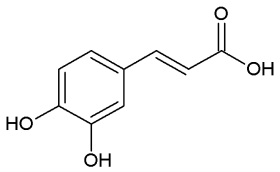
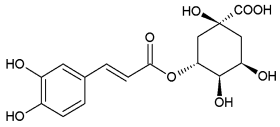
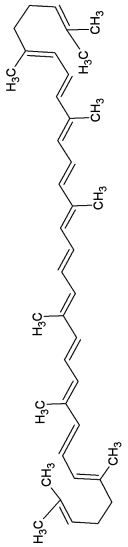
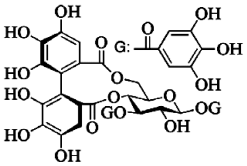
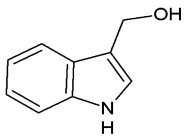
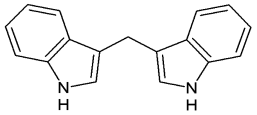
1	2	3	4	5	6
Coffee polyphenols: caffeic acid, chlorogenic acid	caffeic acid  chlorogenic acid 	*Coffea arabica*, and the "robusta" form of hardier *Coffea canephora*	antimicrobial, anti-adsorption, anti-adhesive, antioxidant, antiradical [134, 135]	MCF-7 and MDA-MB-231 breast cancer cells	decrease in RARβ2 promoter methylation; catechol-O-methyltransferase (COMT)-mediated methylation results in the depletion of the methyl donor SAM and the formation of SAH, which is a potent feedback inhibitor of DNA methylation [136]
Lycopene		tomatoes and tomato products, rosehips, pink grapefruit, guava, apricots	antioxidant, anti-proliferation, anti-cancer, anti-invasive and anti-metastatic [137]	MDA-MB-468 cells	reactivation of GSTP1 mRNA expression, associated with reduced promoter methylation
				MCF10A human breast cancer cells	downregulation of RARβ and HIN1 promoter methylation [138]
Ellagitannin		raspberries, strawberries, almonds, and walnuts	antioxidant, antiviral, antimicrobial, antimutagenic, anti-inflammatory, anti-proliferative [139]	HepG2 cells	upregulation of let-7e, miR-370, miR-373, and miR-526b; downregulation of let-7a, let-7c, let-7d [140]
Indole-3-carbinol (I3C), diindolylmethane (DIM)	indole-3-carbinol  diindolylmethane 	Cruciferous vegetables such as broccoli, cabbage, Brussels sprouts, cauliflower, radish, and mustard	antiproliferative, anti-inflammation, anticancer, pro-apoptotic [141]	gemcitabine-resistant human pancreatic cancer cell, MiaPaCa-2, Panc-1, and Aspc-1	DIM results in upregulation of members of the *let-7* (*let-7b*, *let-7e*) and miR-200 families (*miR-200b*, *miR-200c*); induced reversal of the epithelial to mesenchymal transition (EMT) phenotype [124]

Table (Contd.)

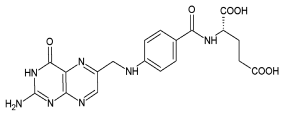
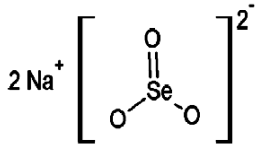
1	2	3	4	5	6
				animal studies	I3C strongly counter-regulates the expression of miRNAs involved in *p53* functions (*miR-34b*), *TGF-β* expression (*miR-26a*), ERBB2 activation (*miR-125a-prec*), and angiogenesis (*miR-10a*) [142]
			Micronutrients and vitamins		
Folic acid		spinach, asparagus, broccoli, beans, peas, lentils, sunflower seeds, almonds	anticancer, antiproliferative, chemoprevention of malignant transformation [143]	animal studies	increase of genomic DNA methylation [144]; folate deficiency increases DNMT1, DNMT3B, MBD2 and MBD4 mRNA and protein levels [145]; increase in SAM/SAH ratio [146]
				human lymphoblastoid cells and peripheral blood cells	folate deficiency led to global increase in miRNA expression; miR-222 identified as overexpressed [147]
Na selenite		sea foods and organ meats, muscle meats, cereals and other grains, and dairy products	antitumor, angiogenesis, anticarcinogen activation and immunomodulatory, anticancer [148]	animal studies	increase of global DNA methylation [149]
				LNCaP cells	decrease in *DNMT* mRNA and protein expression; reduced global DNA methylation, and re-expression of *GSTP1*, *APC* and *CSR1* associated with reduced *GSTP1* promoter methylation; inhibition of *HDAC* activity and increase in ac-H3 levels, but lowered methylation at H3K9 [150]

Table (Contd.)

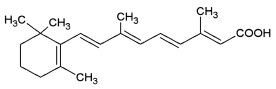
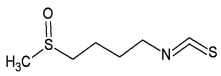
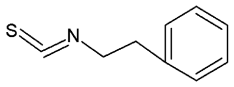
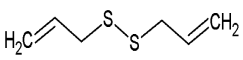
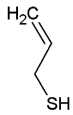
1	2	3	4	5	6
Retinoic acid		Vietnamese gac, crude palm oil, yellow and orange fruits (mango, papaya), orange root vegetables (carrots), spinach, sweet potatoes	anticancer, antiproliferative, differentiating, pro-apoptotic [151]	SiHa cervical squamous carcinoma	decrease in DNA methylation efficiency [152]
				MKN-45 gastric cancer cells	inhibition of AP-1 activity, down-regulate AP-1 responsive genes, including *DNMT1* and decrease DNA methylation [153]
				non-invasive MCF-7 cells	reduction in promoter methylation and an increase in the expression of *RARβ2* and *PTEN* tumor suppressor genes [154]
				neuroblastoma SK-N-BE, SH-SY5Y cells	downregulation of methyltransferases DNMT1 and DNMT3B, along with the upregulation of endogenous miRNAs targeting these DNMTs [155]
				NB4 acute promyelocytic leukemia cells	upregulation of miRNAs including miR-15, miR-16 and several members of the let-7 family [156]
Sulfur-containing compounds					
Sulforaphane (SFN)		cruciferous vegetables, such as broccoli and broccoli sprouts as well as cauliflower	antioxidant, anti-inflammatory, and anticancer; agent of defense against diabetes, ocular disorders [157]	human BPH-1, LNCaP and PC-3 prostate epithelial cells	increase in global acetylation of histone H3 and H4, accompanied by locus specific hyperacetylation of H3, H4 or both at the *p21* promoter [158]
				MCF-7 and MDA-MB-231 human breast cancer cells	inhibition of telomerase activity and repressed *hTERT* mRNA expression associated with downregulation of *DNMT1* and *DNMT3a* protein expression and a significant reduction in *hTERT* [159]

Table (Contd.)

1	2	3	4	5	6
Phenethyl isothiocyanate		cruciferous vegetables such as watercress, radishes and turnips	angiogenesis inhibitor, antiproliferative and proapoptotic, antimutagenic, anticancer, antioxidant [160]	LNCaP cells	enhancement of histone acetylation, cell cycle arrest, and *p53*-independent upregulation of cyclin-dependent kinase inhibitors, including *p21WAF1* and *p27* [161]
				animal studies	counter-regulation of the expression of 18 out of 25 miRNAs downregulated by environmental cigarette smoke (ECS) [162]
Diallyldisulfide (DADS) and allylmercaptan (AM)	diallyl-disulfide  allyl-mercaptan 	garlic, onions, leeks and other *Allium* vegetables	antitumor, antimicrobial, antifungal, antivirus, antithrombotic, anti-hypotension and immune modulation effects [163]	HT29 human colon adenocarcinoma cell	*HDAC* inhibition led to increased global ac-H3 and ac-H4, enhanced ac-H3 binding to the *p21* promoter, upregulation of *p21*, and cell cycle arrest [164, 165]

lated markers at H3K27, H3K9, and H3K4 on six selected genes including *SRC3* (steroid receptor coactivator protein 3 that displays HAT activity), *BRCA1*, *ER-α*, *ER-β*, *EZH2* (histone-lysine N-methyltransferase that adds methyl group to H3K27), and *p300* [120].

When genistein is added to HT29 cell line, it showed significant inhibitory effects on HDAC activity with potent inhibitory IC_{50} concentration of 97 ± 18 μM [77]. However, treatment of HT29 cells with high concentration (200 μM) of genistein was associated with downregulation of HDAC1 protein. Likewise, treatment of KYSE510 esophageal squamous carcinoma cells with 5 and 100 μM genistein induced HDAC activity inhibition of 13.2 and 33%, respectively, resulting in reversal of promoter hypermethylation of *p16*, *RARβ2*, and *MGMT* (O6-methylguanine methyltransferase) and thus gene re-expression [121].

Genistein showed significant reversal of promoter hypermethylation and reactivation of tumor suppressor gene *BTG3* in prostate carcinoma cell lines LNCaP and PC3 as well as in renal cell carcinoma cell lines A498, ACHN, and HEK-293, associated with increased level of histone acetylation and binding of RNA polymerase II with the promoter of *BTG3* gene resulting in the formation of active chromatin, while in squamous cervical cancer cell line SiHa it was found to be associated with promoter demethylation of *RARβ2*, a tumor suppressor gene, and thus led to gene reactivation [122].

In addition to the effect of genistein on histone modifications, particularly histone acetylation and methylation, it also influences DNMTs *in vitro* at protein expression level and by inhibiting DNMT1 activity as well. It downregulates methylation status specifically at tumor suppressor genes *p21* and *p16* promoter, thereby affecting survival of cancerous cells [123].

Genistein can reactivate the gene silenced by methylation in breast cancers not only by DNMT1 activity inhibition, but also via downregulating DNMT1 protein level. In MCF-7 and MDAMB-231 cell lines, it was shown to significantly inhibit HDAC1 but also to decrease DNMT1 and MeCP2 protein levels associated with decreased transcription expression of *DNMT1*, *DNMT3a*,

and *DNMT3b*. In addition, treatment of breast cancer with a low concentration (3.125 μM) of genistein resulted in demethylation at the *GSTP1* gene promoter.

The intrinsic synergistic/additive effect by genistein may be associated with its inhibitory effects on DNMTs and HDACs together. Genistein-mediated hypomethylation and hyperacetylation associated with reactivation of silenced PTEN tumor suppressor gene expression in prostate cancer cells. In addition, genistein has also been shown to regulate the expression of miRNA, an epigenetic marker, and their targets in several cancer types [124, 125]. Other natural compounds that have been found to be of importance in the reversal of epigenetic changes are mentioned in the table.

CONCLUSION AND PROSPECTS

Alterations in epigenetic modifications regulating essential cellular processes required for maintaining cellular identity have been found to be associated with cancer. Studies discussed in this review have shown that dietary chemopreventive agents can reverse these abnormal epigenetic alterations by affecting global DNA methylation accompanied by reactivation of tumor suppressor genes silenced by promoter hypermethylation, upregulating genes by altering histone covalent modifications as well as miRNA, and thus they could be considered as chemotherapeutic agents for cancer therapy. This characteristic has resulted in increasing enthusiasm for developing therapeutic strategies by targeting various epigenetic factors such as HDAC, HAT, DNMTs, and miRNAs by natural compounds either alone or in combination with similar compounds having structural and functional similarity. However, further investigations of other natural compounds as effective therapeutic epigenetic agents need to fully explore the potential of these compounds in the treatment of cancer and other diseases as well as those based on structure–activity relationship.

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